REMARKS

I. Status of Claims

Upon entry of this amendment, claims 30, 32 and 38-50 are pending. Claims 30, 32, 41, and 42 have been amended. Claims 43 through 50 are newly added.

To expedite prosecution, claims 30, 41, and 42 have been amended to clarify the presently preferred embodiment. Support for these amendments is found throughout the specification.

Claim 30 has been amended to correct a typographical error.

Support for new claims 43 and 47 is found throughout the specification, in particular, in original claim 32, paragraph [0033] of US2005/0227917, and paragraph [0144] of US2005/0227917.

Support for new claims 44-46 and 48-50 is found throughout the specification, in particular, in original claims 11 - 13.

As no new matter was added by this amendment, entry of the amendment is respectfully requested.

Amendment and cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented.

II. Claim Rejections Under 35 USC §112, Second Paragraph

Claims 30, 32, and 38-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office alleges that the intended meaning of the preamble is not clear and further, that claim 32 is indefinite because it depends from a canceled claim.

Applicants respectfully submit that in view of the amendments, this rejection is now moot. Withdrawal of the rejection is thus respectfully requested.

III. Claim Rejections Under 35 USC §112, First Paragraph- Lack of Enablement

Claims 30, 32, and 38-42 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office maintains that the subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Overview

To the extent that the rejection applies to the amended claim set, Applicants respectfully maintain traversal of the rejections and its supporting remarks.

Applicants respectfully assert that the currently pending claims have more than adequate support in the specification to enable one of skill in the art to make and use the claimed invention without undue experimentation. For example, the specification teaches that SEQ ID NO: 23702 expression data and expression data from at least one molecular marker gene can be easily obtained from a patient sample by various known methods, such as contacting the sample with probes specific for the nucleic acid comprising the nucleotide sequence of SEQ ID NO: 23702 and for the at least one molecular marker gene (see paragraph [0127]); and that the expression data of SEQ ID NO: 23702 can be used in combination with the expression data of the at least one molecular marker gene to assess the risk of having cancer (see paragraph [0632]) by comparing the expression data from a patient sample to a control level of expression of SEQ ID NO: 23702 and a control level of expression of the at least one molecular marker gene (see paragraph [0144]). Further, several working examples in the specification disclose the use of differentially expressed genes as a risk assessment tool to be used in combination with other methods for evaluating a patient's cancer phenotype. Paragraph [0632] embodies this practice by stating "The differential expression of these polynucleotides can be used as a diagnostic marker, a prognostic marker, for risk assessment, patient treatment and the like. These polynucleotide sequences can also be used in combination with other molecular and/or biochemical markers."

Moreover, working Example 105 (in particular, see paragraphs [1168] and [1169]) shows that metastatic and primary tumor colon cancer cells have a statistically significant two-fold over-expression of SEQ ID NO: 23702 as compared to a control level of SEQ ID NO: 230702

expression in matched and unmatched controls. Example 105 further shows that breast and prostate cancerous cells from patient tumor samples also have a statistically significant at least two-fold over-expression of SEQ ID NO: 23702 as compared to control levels of expression of SEQ ID NO: 23702 in matched controls.

Thus, the teachings in the specification and the data presented in Example 105 clearly teach one of skill to practice methods using the expression level of nucleic acids comprising SEQ ID NO: 23702 in combination with the expression level of at least one molecular marker gene to assess whether there is an increased risk that a patient has colon (primary tumor or metastasized), breast, or prostate cancer without undue experimentation.

Data

The Office alleges that the data found in the application is "very limited compared to the breadth of the claims" (Office Action, page 8). Applicants respectfully remind the Examiner that a specification need not contain a working example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples is only one factor to be considered in the enablement analysis.

Below, Applicants address the Office's primary allegations:

1) The Office alleges that the claims are not enabled because they are directed to any sample containing breast, colon, or prostate cells while only tissue samples obtained by LCM were analyzed (*See* Office Action, page 8).

As noted above, all that is required for enablement is that the specification teach one of skill to practice the claimed invention without undue experimentation. The expression level of a nucleic acid comprising SEQ ID NO: 23702 in tissue samples necessarily reflects the expression levels in the cells making up the tissue. Therefore, practicing the claimed methods of risk assessment on samples which contain cells of the specified tissue types, ranging from intact tissue to blood samples containing circulating cells, is fully enabled by the teachings in the specification regarding tissue samples.

2) The Office alleges that the example does not pertain to risk assessment because only patients known to have breast, colon, or prostate cancer were included in the study (*See* Office Action, page 8).

Specifically, the Examiner asserts that "analysis of a control samples from cancer-free individuals is necessary to establish a correlation between the expression level of a nucleic acid comprising SEQ ID NO: 23702 and cancer" (Office Action, page 21). As support for this allegation, the Office cites to two articles which purportedly show that colon cancer alters gene expression levels in apparently normal colon tissue from colon cancer patients.

Applicants agree that if the teachings of the articles are as described by the Office, they demonstrate that the controls from the morphologically normal tissue of the colon cancer patients having cancer of that tissue type are not equivalent to those from healthy, colon cancer-free individuals. However, this lack of equivalence does not detract from the significance of data demonstrating that SEQ ID NO: 23702 is differentially expressed in cancerous tissue as compared to morphologically normal tissue. The danger of using morphologically normal tissue from cancer patients is that similarity between the gene expression patterns in tissue which is morphologically normal, yet genetically altered in a way similar to cancerous tissue, will mask the identification of sequences which are differentially expressed between cancerous and non-cancerous tissue. Contrary to the Office's assertion, the danger is not that the sequences identified as differentially expressed are non-specific to cancer. Comparison to genetically altered, yet morphologically normal matched or unmatched controls raises the bar such that any sequences identified as being differentially expressed are those which have expression patterns differing so widely that they are detectable above the background noise of the altered expression pattern of morphologically normal, yet genetically altered tissue.

The use of the matched controls allowing the individual be compared to self provides further advantages in that it eliminates interference from natural variations of expression between individuals which could result in both false negatives and false positives.

Thus, in view of the above, Applicants respectfully submit that the data provided in Example 105 establishes a correlation between an increased level of nucleic acids comprising SEQ ID NO: 23702 and colon (primary tumor and metastasized), breast, or prostate cancer.

3) The Office alleges that the number of patients in study is rather small, and the total number of patients in the studies for all cancers is not clear. For the five rows of the data in Table 159, it is not clear whether the different experiments were conducted using different nucleic acids isolated from the same set of 23 patients or from different sets of patients (*See* Office Action, page 8).

Applicants respectfully assert that it is irrelevant whether the different experiments in Table 159 were conducted using nucleic acids isolated from the same patients or from different patients. Even if the experiments were conducted on the same patients, the number of patients tested for each cancer is more than sufficient to support the pending claims.

4) The Office alleges that there is no discussion of the significance of the observed results, such as a P-value calculation. (*See* Office Action, page 9).

Contrary to the Office's statement, the specification discusses the significance of the results. As noted in the last sentence of paragraph [1166], the database tables were populated using a 95% confidence level ($p>0.05$). Thus, the tables express as a percentage of the total number of patients in which a SEQ ID was over-expressed at a statistically significant level by at least two fold.

State of Prior Art and Unpredictability

The Office continues to assert that there is a high degree of unpredictability with respect to the claimed methods, in particular, asserting that it is entirely unpredictable whether or not the expression level of a particular gene can be used to detect cancerous cells or assess a subject's risk of having cancer. The Office further asserts that the wide variation in the number of patients showing a two-fold increase both between and within the cancer types tested and the small number of patients in the studies supports the conclusion that the claimed methods are unpredictable.

Applicants respectfully maintain that this variability in the data between and within cancer types is irrelevant. The claims are directed to assessing the ***risk*** of having the cancers of interest. Methods which assess risk by detection of the expression level of a nucleotide sequence involve assessing the probability that patient has cancer; they do not require conclusively determining whether a patient has cancer.

Probability is influenced the frequency at which events happen under particular circumstances. Therefore the variation within cancer types that the Office is concerned about is irrelevant to assessing the risk of whether a patient has the cancer of interest. Any significant overexpression of SEQ ID NO: 23702 in cancerous colon, breast, and prostate cells in any percentage of patients, however low or variable, teaches that there is an increased frequency of overexpression in cancer patients, and accordingly, that detection of SEQ ID NO: 23702 in a patient sample indicates there is an increased risk that the patient has that cancer type. This establishes that there is a correlation between increased levels of SEQ ID NO: 23702 and the cancers of interest. The correlation may not be a one to one correlation, such that every sample containing cells from a patient suspected of having cancer will have increased expression of SEQ ID NO: 27302 as compared to a control, but it is a correlation nonetheless. In addition, at least a portion of the variation between and within cancer types is a reflection of technical limitations of the experiment rather than a weak correlation between the overexpression of SEQ ID NO: 23702 and the cancers of interest. The experiments in Example 105 were conducted using non-standardized microarrays, which are vulnerable to manufacturing defects that lead to false negatives. Paragraph [1162] of the application describes how the microarrays were constructed using polynucleotides obtained from both publicly available sources and from cDNA libraries generated from selected cell lines and patient tissues as described. Finally, variation between the cancer types tested, even that which is independent of technical limitations, is irrelevant to methods for assessing the risk of a patient having the cancers of interest. Tissues vary widely in their properties and mechanisms of carcinogenesis. Accordingly, variation in percentage of overexpression between cancers is expected, and fails to speak to unpredictability of the claimed methods. Applicants have provided data demonstrating that SEQ ID NO: 23702 is overexpressed in a certain percentage of patients having the each of the cancers to which the pending claims are

directed - breast, prostate, and colon cancer (both primary tumor and metastasized). As discussed above, this is sufficient to establish a correlation between increased levels of SEQ ID NO: 23702 and the cancers of interest.

Conclusion

In view of the above, Applicants respectfully submit that a person skilled in the art would be able to assess the increased risk of colon, breast, or prostate cancer based on the overexpression of SEQ ID NO: 23702 and the change in level of expression of at least one molecular marker gene using the teachings of the present application without undue experimentation. Applicants thus respectfully request that this basis for rejection be withdrawn.

IV. Withdrawal of Objections/Rejections

Applicants thank the Examiner for withdrawing the objection to claim 9, and agreeing that the indefiniteness rejection of the claim 36 and the written description rejections of claims 7, 9, 11-13, 30-32, and 34-47 are moot in view of the amendments.

V. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **Docket No. 223002106600**.

However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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